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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,571	09/11/2001	Kenneth R. Chien	041673-1001	7236

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/954,571	CHIEN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-72 and 77-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-72 and 77-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 12/14/06 has been acknowledged.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/15/06 has been entered.

Claims 70-72 and 77-97 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims *70-72 and 77-97* are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for delivering a therapeutic dose of a transdominant negative phospholamban (S16E PLB) to enhance SERCA-2 activity in order to treat cardiac contractility and reduce the reoccurrence of interstitial fibrosis by intra-coronary gene administering an AAV encoding transdominant negative phospholamban containing a mutation at amino acid 16 from serine (S) to glutamic acid (E), does not reasonably provide enablement for a method of delivering a therapeutic

dose of any other PLB mutant, which is capable of treating any cardiac disease caused by any and all factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 02/15/06.

Nature Of Invention:

The instant invention relates to treatment of heart failure via a method of gene therapy using mutated form of phospholamban gene.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope invention as claimed encompasses a method of transducing cardic muscles in a patient by administering a viral vector encoding any mutated phospholamban gene (PLB) in order to treat heart failure associated with any etiology. The specification teaches the expression of dominant negative phospholamban disrupts the function of the wild type protein. The specification teaches an adeno-associated vector (AAV-S16EPLB) that encodes a phospholamban transdominant mutant S16EPLB by replacing Ser16 with the basic amino acid glutamine, thereby introducing a negative charge at position 16. At best the specification teaches intra-coronary administration of the AdenoS16EPLB significantly enhanced cardiac contractility indicated by an approximately 33% increase in mean velocity of circumferential fiber shortening (mVcf) 6 days after transfection (example-7). Besides increasing cardiac contractility by an intra-coronary administration of the AdenoS16EPLB, the specification fails to disclose the treatment of heart failure caused by factors other than phospholamban and SERCA-2 interaction.

State Of Art And Predictability:

The scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy (see Juengst BMJ, 326:1410-11, 2003; Check NATURE 422:7, 2003; Couzin et al, SCIENCE 307:1028,

2005; Rosenberg et al, SCIENCE 287:1751, 2000; Anderson, NATURE 392:25-30, 1998; Touchette, NAT. MED. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectation of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

In instant case the state of the art regarding the "phospholamban hypothesis" in heart failure is complex and highly unpredictable, since phospholamban erasure does not cure hypertrophy or overall ventricular function in the setting of experimental heart failure due to over expression of tropomodulin Gαq or a mutant myosin binding protein C, although the characteristically prolonged cardiomyocyte calcium transients and enhanced unloaded fractional shortening were rescued. Furthermore phospholamban ablation only incompletely healed a mouse model of hypertrophic cardiomyopathy due to expression of a mutant myosin heavy chain, and did not improve the progressive demise of the pressure-overloaded mouse heart resulting from chronic aortic stenosis. Therefore the heart failure is more likely a clinical entity characterized largely by its overwhelming complexity rather than by the instigating cause(s), it starts to seem unlikely that one single approach (e.g., phosholamban antagonism) will ever benefit all cases of human heart failure. A uniform conclusion that does emerge from these efforts is that we still have very limited understanding about the full complexity of one single aspect of heart muscle physiology (calcium handling), let alone the exponential complexity of human heart disease in general (see Armand et al CARDIOVASC RES. 62(3):439-41. 2004, Janczewski et al CARDIOVASC RES. 62(3):468-80, 2004).

In instant case the scope of instant invention encompasses the treatment of heart failure by administering any viral vector encoding any mutant of phospholamban gene. Considering the complexities involved the etiology of heart failure instant specification fails to provide an enabling disclosure, which establishes any mutant form of phospholamban gene is capable of treating heart failure.

For example considering the instant specification is it is unclear how one skill in the art would treat heart failure of ischemic origin by administering a mutant phospholamban gene to the cardiac muscles. The RAC advisory panel clearly emphasized the need for a greater understanding of an underlying mechanism that contributes to a disease along with the pathogenesis of the disease. The state of the art at the time of filing was such that the heart failure is almost always a chronic, long-term condition, although it can sometimes develop suddenly. This condition may affect the right side, the left side, or both sides of the heart. The factors that leads to heart failure include family history (congenital heart disease), Ischemic heart disease/Myocardial infarction (coronary artery disease), Heart muscle disease (dilated cardiomyopathy, hypertrophic cardiomyopathy) or inflammation (myocarditis), Arrhythmia, Hypertension, Cardiac fibrosis, Coarctation of the aorta, Aortic stenosis/regurgitation, Mitral regurgitation, Pulmonary stenosis/Pulmonary hypertension/Pulmonary embolism all leading to cor pulmonale and Mitral valve disease, arrhythmia or dysrhythmia (*See Lip et al, BMJ* 320:104-107, 2000).

It remains unclear whether phospholamban inhibition is effective in all forms of heart failure. It has been reported that PLN ablation enhances sarcoplasmic reticulum calcium cycling and cardiomyocyte contractility at the single-cell level in these mouse models, although it does not seem to prevent heart failure progression (See Chien et al Nat Med. 9(5):508-9, 2003, page 509, col.1 para. 4).

In instant case besides the use of a phospholamban transdominant negative mutant S16EPLB the specification fails to disclose any other phospholamban mutant, which is capable of enhancing SERCA-2 activity leading enhanced cardiac contractility. Furthermore the scope invention as claimed encompasses any PLB mutant. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Therefore besides S16E PLB, it would requires an undue amount of experimentation to

characterize any other transdominant negative mutant of phospholamban for the required therapeutic biological activities.

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In addition there exists an uncertainty about the degree to which a vector's genetic material may integrate into the host genome extends to most types of gene therapy trials. Scientists are also unsure how an insertion could affect a patient, and worry cancer could occasionally be triggered, such as occurred various trials involving gene therapy (see Check Nature 422:7, 2003). Thus the use of any viral vector especially in context with cardiac gene transfer is considered unpredictable and would require further undue amount of experimentation. Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals. In the instant case the specification as filed discloses intra-coronary administration of adeno-associated vector (AAV-S16EPLB) that leads to gene delivery to heart muscles.

In instant case treating a heart failure via a gene based therapy is not considered routine in the art and without sufficient guidance to a heart failure associated with all etiologies and transdominant activity of the mutated phosholamban gene (as claimed)

the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. see in re wands 858 f.2d 731, 8 uspq2nd 1400 (fed. cir, 1988). it is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. see ex parte Singh, 17 uspq2d 1714 (bpai 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633